IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OKLAHOMA

IN RE: GENENTECH, INC.,	)	
HERCEPTIN (TRASTUZUMAB)	)	MDL DOCKET NO. 16-MD-2700
MARKETING AND SALES	)	
PRACTICES LITIGATION	)	

OPINION AND ORDER

Before the Court is the Amended Motion for Summary Judgment Based on Federal Preemption (Doc. 201) filed by defendant Genentech, Inc. ("Genentech"). Plaintiffs oppose the motion.

I. Introduction

Genentech manufactures, markets and distributes Herceptin® (hereafter, "Herceptin"), a biologic drug used to treat breast cancer. Plaintiffs are cancer treatment providers who have purchased Herceptin for treatment of their patients. Plaintiffs do not challenge the efficacy or safety of the drug, but contend that Herceptin's labeling is misleading because, although the Herceptin label states that each vial contains 440 mg of Herceptin at a concentration of 21 mg/mL, not every vial contains that amount or more. They assert California state law claims for breach of express and implied warranties and unjust enrichment, and they seek actual damages, costs and attorneys' fees. Doc. 45 at 13-20. Genentech, in its Motion for Summary Judgment, contends that Plaintiffs' claims are preempted by federal law.

II. Background

Federal law gives the Food and Drug Administration ("FDA") the authority and responsibility to regulate prescription drugs. *See* 21 U.S.C. § 301 *et seq*. The FDA regulates virtually every aspect of the manufacturing, distribution, evaluation and labeling of drugs marketed and sold in the United States. *See Bruesewitz v. Wyeth LLC*, 562 U.S. 223, 237 (2011) (noting pervasive regulation of vaccine licensing). The FDA drug approval process is "onerous and lengthy." *Mutual Pharm. Co., Inc. v. Bartlett*, 570 U.S. 472, 476 (2013).

Biologics[1] such as Herceptin are similarly regulated. *See* 21 U.S. § 321(g)(1). Before a biologic product can be distributed, the FDA must approve the sponsor's biologic license application ("BLA"). 21 U.S.C. § 355(b), 42 U.S.C. §262(a). The BLA contains "specifications" for the product, which establish criteria for determining whether each lot of the biologic satisfactorily conforms to the drug product, as approved by the FDA. 21 C.F.R. § 211.165(a). It also includes data from studies showing that the product meets prescribed requirements for safety, purity and potency; a full description of manufacturing methods; data establishing product stability; samples of the product, labeling, and containers; and summaries of product test results. *Id.*, §§ 601.2(a), 600.3(kk). Manufacturers of biologic products are required to test each lot of the product for, *inter alia*, potency, safety, purity and sterility. *Id.*, §§ 610.10, 610.12-14. If a lot does not meet the specifications, it cannot be distributed to the public and must be rejected. *Id*., § 211.165(f).

The FDA will approve a BLA only if it determines that the manufacturer's biological product and facilities comply with federal regulations. *Id.*, § 601.4. Essentially, a biologics license

[1] Biologics are drugs made from complex molecules manufactured using living microorganisms, plants or animal cells.

reflects the FDA's determination that the product is safe, pure and effective, and that the manufacturer's facilities and processes are adequate to meet these high standards. *Id.*, § 601.2(d).

The biologic product's accompanying labeling must also conform to federal law. 21 U.S.C. §§ 331(a), 352; 21 C.F.R. § 601.2(a). The FDA will approve a BLA only if it finds that the drug is "safe for use" under the conditions "prescribed, recommended, or suggested in the proposed labeling," and it will approve the labeling only if it is not "false or misleading in any particular." 21 U.S.C. § 355(d)(1) & (7).

Additionally, applicants must notify the FDA about "each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application(s)." 21 C.F.R. § 601.12(a). Prior FDA approval is usually required for labeling changes, particularly if the proposed change would affect the information that must appear in the Highlights of Prescribing Information section of the physician package insert. *Id.*, § 601.12(f)(1) (citing § 201.57(a)).

III. Statement of Undisputed Material Facts

Twenty to thirty percent of breast cancers are known to have amplification of a growth factor receptor gene known as HER2, and women whose breast cancers have a high level of expression of this gene have a shortened survival rate. Doc. 201-2, Def. Ex. 2 at 7. Herceptin—known generically as trastuzumab—is a prescription drug that helps stop the cancer's growth by targeting HER2 protein. Doc. 201-1, Def. Ex. 1 at 2. Trastuzumad's effect in fighting this aggressive form of cancer has been described as "dramatic," and trials have shown that addition of the drug to chemotherapy "resulted in a remarkable 50% reduction in disease recurrence compared with patients receiving chemotherapy alone." Doc. 201-3, Def. Ex. 3 at 3, Korkaya, H.,

et al., *HER2 and Breast Cancer Stem Cells: More than Meets the Eye*, 73 *Cancer Research* 3489-93 (June 15, 2013)).

Herceptin is a biologic product produced from living organisms—namely, Chinese hamster ovary cells that have been genetically modified to produce trastuzumab, the active ingredient. Doc. 201-5, Def. Ex. 5, Dec. of Dr. David T. Lin, ¶30; Doc. 201-6, Def. Ex. 6, Dec. of Dana L. Swisher, ¶¶ 5-7. Its production begins in large bioreactor tanks with modified cells replicating in a culture medium and producing trastuzumab. *Id.*, Swisher Dec., ¶ 7. Eventually, the protein trastuzumab is harvested from the cells, a process involving several purification steps to remove cell debris and other unwanted elements. *Id.* The resulting protein solution is referred to as the "drug substance." *Id.* The drug substance is tested to ensure the protein concentration is within the FDA-approved range of 25 milligrams per milliliter (mg/mL), plus or minus 1 mg/mL. *Id.*, ¶ 8. If the drug substance concentration is outside the approved range, the batch is rejected. *Id.* If it is within the approved range, it is frozen for storage and shipping. *Id.*

Tanks of frozen Herceptin drug substance are shipped to manufacturing facilities, where they are thawed and tested again to ensure the concentration is still within the FDA-approved range of 25 mg/mL ± 1mg/mL. *Id.*, ¶9. From there, one or more tanks of Herceptin substance may be pooled. *Id*. Generally, the next step prior to filling is sterile filtration. *Id.*, ¶10. During this step, the drug substance passes through a sterilization-grade filter and on to the fill line. *Id.* The drug substance is then filtered, sterilized and dispensed into glass vials by filling machines. *Id.*, ¶ 11. The target fill weight for each vial is 17.92 grams, but the FDA-approved acceptable outer range is 17.56 to 18.28 grams, *i.e.* 17.92 g ± 2%. *Id*. A range around the target fill weight of 17.92 grams is necessary because the filling equipment is incapable of filling every vial with precisely 17.92 grams. *Id*.

The vials of drug substance are lyophilized or freeze-dried, removing most of the water and leaving what is known as the Herceptin "cake," comprised of the dry solid protein and some inactive ingredients. *Id.*, ¶12. The FDA-approved specification for protein content of the drug product is 440 mg± 35mg/mL per vial. *Id.*, ¶12. After the vials are filled and sealed, sample vials are submitted to Quality Control, where they undergo final testing prior to release for distribution. *Id.*, ¶13. The sample vials are identified in the Certificate of Analysis ("COA"). *Id.* The protein content of the vials is tested in accordance with protocol Q12398. *Id.* ¶¶13, 16.

Because the precise concentration of the drug substance and the precise fill weight varies from batch to batch, the weight of the Herceptin cake in each vial will also vary in a range around 440 mg. *Id*., ¶ 14. When shipped, each vial of Herceptin is accompanied by a vial of sterile water that providers use to dissolve the powder cake—a process known as reconstitution. *Id.*, Doc. 201-1, Ex. 1, Highlights of Prescribing Information.

The FDA approved the BLA for Herceptin on September 25, 1998. Doc. 201-4, Def. Ex. 4. The BLA provides for Herceptin drug substance concentrations within a range of 25 mg/mL ± 1mg/mL and drug product levels within a range of 440 mg ± 35 mg. *Id.* The FDA also approved Herceptin labeling that claimed 440 mg per vial, recognizing in subsequent correspondence with Genentech that the "expected recovery from each vial is approximately 19 mL or 400 mg." Doc. 377-1, Def. Ex. 13. Additionally, in 1999, the FDA drafted a letter to providers explicitly referring to the fact that the vials were designed to deliver 400 mg. Doc. 201-5, Def. Ex. 5, Lin Dec., ¶¶47-49 (citing Def. Ex. 13, *supra*). US Pharmacopeia ("USP") General Chapter <905>, *Uniformity of Dosage Units,* provides for an allowable variation of 15 percent from the stated weight. *Id.*, Lin Dec., ¶ 29 and Ex. D thereto, p. 494, Table 2.

Plaintiffs' own data show that:

- Herceptin drug substance concentrations have always complied with the FDA-approved range of 25 mg/mL ± 1 mg/mL, and
- Herceptin drug product levels always complied with the FDA-approved range of 440 mg± 35 mg.

Doc. 368, Pls.' SOF 5, 10, 26.

The term "nominal" in prescription drug labeling refers to a "theoretical" amount, signaling that the actual amount in each vial will vary. Doc. 201-5, Def. Ex. 5, Lin Dec., ¶ 36; Doc 377-2, Def. Ex. 14 at 145:20-146:8.

The Prescribing Information[2] states that Herceptin is shipped in multi-dose vials "nominally containing 440 mg Herceptin as a lyophilized, sterile powder." Doc. 201-1, Def. Ex. 1, Highlights of Prescribing Information at 1. Similarly, the carton for each vial states that "the nominal content of each HERCEPTIN vial is 440 mg Trastuzumab." *Id.*, Doc. 201-7, Def. Ex. 7. This description in labeling is consistent with the FDA-approved specification of 440 mg ± 35 mg and the variability permitted under FDA regulations. *Id.*

The Herceptin carton and vial labels state that reconstitution will "yield a multiple-dose solution containing approximately 21 mg/mL Trastuzumab." 201-7, Def. Ex. 7; Doc. 201-8, Def. Ex. 8. The concentration is "approximately" 21 mg/ml because the actual concentration depends on the amount of Herceptin in each vial, which varies, and the amount of sterile water a provider injects during reconstitution, which also varies. Doc. 201-5, Def. Ex. 5, Lin Dec., ¶¶ 38-40, 43. Additionally, each vial of Herceptin contains a residual and variable amount of moisture—up to three percent—that may be lost over time due to absorption by the stopper on the vial. *Id.*, ¶ 33.

[2] Prescribing Information is a detailed description of a drug's uses, dosage range, side effects, drug-drug interactions and contraindications that is available to clinicians and included in pharmaceutical packaging instructions.

For each year from 2000 through 2008, a majority of the Herceptin batches released in the United States contained at least 440 mg of trastuzumab. Doc. 368 at 16, Pls. SOF 10. In 2000, 2001, and 2006, more than 82 percent of Herceptin batches contained at least 440 mg of trastuzumab, and in 1998 and 2005, 100 percent of batches met or exceeded the label claim. *Id.* Pls.' SOF 11. However, the proportion of batches containing at least 440 mg of trastuzumab dropped below 50 percent by 2009 and has not exceeded 50 percent since then. *Id.*, Pls. SOF 10. Only one of the 125 batches tested in the three-year period of 2012-2014 contained at least 440 mg of trastuzumab per vial, and in 2012 and 2014, none of the 89 Herceptin batches tested contained 440 mg or more. *Id.*, Pls. SOF 10-11, 14. Nevertheless, at no time from 1998 to 2017 did *any* batch contain less than the lower limit of 405 mg of trastuzumab approved by the FDA. Doc. 201-6, Def. Ex. 6, Swisher Dec., ¶14.

Between the FDA's initial approval of Herceptin on September 25, 1998, and February 3, 2017, the FDA approved more than 10 supplemental applications from Genentech proposing revisions to the Herceptin Prescribing Information without ever directing Genentech to change the description of net weight or concentration. Doc. 201-5, Def. Ex. 5, Lin Dec., ¶ 50. For example, on October 12, 2012, Genentech submitted a prior approval supplement to the FDA requesting approval for the Hillsboro Technical Operations manufacturing facility to manufacture 440 mg vials. Doc. 377-13, Def. Ex. 25. The supplement included data on three qualification batches of Herceptin drug product, and the protein content for all three batches was below 440 mg. Doc. 377-14, Def. Ex. 26. The FDA approved the supplement on February 14, 2013. Doc. 377-15, Def. Ex. 27. On June 6, 2014, the FDA approved a supplement for a manufacturing facility, that also included data on three qualification batches for which the protein content was below 440 mg. Doc. 377-16, Def. Ex. 28.

In March 2014, the FDA published a Draft Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products. Doc. 370-31, Pls. Ex. 31. The Draft Guidance stated that "with respect to allowable excess volume, the sponsor/applicant of drugs in ampules or vials, intended for injection must follow the requirements in 21 CFR 201.51(g)."[3] The Draft Guidance was finalized in June 2015. Doc. 370-34, Pls. Ex. 34.

On October 30, 2014, after the FDA received complaints from an unidentified oncology pharmacy specialist and other oncology institutions about the inability of end users to withdraw a full 21 mL volume from a vial of Herceptin, FDA and Genentech representatives conducted a teleconference. Doc. 201-9, Def. Ex. 9 at 2. During the teleconference, the FDA asked Genentech to provide a formal written response addressing the FDA's concerns regarding labeling of the Herceptin 440 mg multi-dose vial. *Id*. at 4.[4] The FDA also proposed that in order to provide further clarity, the Herceptin 440 mg label should be revised to reflect the maximum amount that can be withdrawn from the vial, in accordance with the agency's interpretation of 21 C.F.R. § 201.51(g), as reflected in the 2014 Draft Guidance for Industry: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products, March 2014. Doc. 201-9, Def. Ex. 9, Resp. to FDA's Comments Regarding Herceptin 440 mg Multi-Dose Vial Fill at October 3, 2014 Teleconference, at pp. 3-4.

[3] 21 C.F.R. 51(g) states, in pertinent part, "In the case of a liquid drug in ampules or vials, intended for injection, the declaration shall be considered to express the *minimum quantity*. . . (emphasis added).

[4] Plaintiffs contend in their Statement of Facts that the FDA "told Genentech 'several times' that the Herceptin 440 mg labeling was 'misleading." Doc. 368 at 33. To clarify, however, the Court notes that the FDA made all such statements during the October 30, 2014, teleconference between FDA representatives and Genentech personnel, and it appears that this was the first time FDA ever raised such concerns. Doc. 370-54, Pls.' Ex. 54 at 3.

Approximately a month later, in its December 5, 2014, response, Genentech proposed the addition of language stating that recovery of Herceptin may be lower when the 440 mg vial is used as a multi-use vial. *Id.* at 4-5. The FDA did not reply to Genentech's response until February 3, 2017—more than two years after Genentech submitted proposed labeling changes. Doc. 201-10, Def. Ex. 10. During that time, in April 2015 and March 2016, it approved two unrelated labeling supplements that did not change the way net contents were described. Doc. 201-5, Def. Ex. 5, Lin Decl., ¶¶ 58, 71 n. 68.

In its February 3, 2017, Advice Letter, the FDA disagreed with Genentech's proposed labeling changes and directed the company to submit a plan to address revision of the labeling from 440 mg per vial to 420 mg per vial on all labeling and to prepare a communication plan to educate healthcare practitioners on the labeling change. Doc. 201-10, Def. Ex. 10.

Genentech submitted a response to the letter on February 10, 2017. *Id.*, Doc. 201-11, Def. Ex. 11. In its response, Genentech agreed to "update the Herceptin USPI of the previously referred to as the '440 mg' strength to the 420 mg strength that reflects the minimally recoverable volume for the Herceptin vial presentation;" to "commit to providing updated carton/container labeling as a Post-Marketing Commitment," and to "provide an updated communication plan at the time the revised carton/container are submitted." *Id.* The FDA approved the supplemental BLA the same day. *Id.*, Doc. 201-12, Def. Ex. 12.

If Genentech were required to ensure that every vial contained exactly (or at least) 440 mg of Herceptin, it would have to either change its manufacturing processes—including filling and lyophilization, and possibly the amount of diluent for reconstitution—and seek FDA approval for a protein content specification that deviates from the currently approved range of 440 mg ± 35

mg., or—as Plaintiffs suggest—stop selling vials that fail to meet the approved range. Doc. 201, Def. Ex. 6, Swisher Dec., ¶ 15; Doc 368 at 68-69.

The manufacture of Herceptin is an aseptic (sterile) processing operation, and substituting steps in an aseptic processing operation is a "major change" requiring FDA approval. Doc. 377, Ex. 17, U.S. BLA Herceptin, GENE-FL0000000527-529, 55521; C.F.R.§ 601.12(b)(2)(vi). Moreover, changing the target fill rate, which is an in-process specification identified in the BLA, also requires prior FDA approval. Doc. 377, Def. Ex. 14, Lin Dep. at 151:1-25; 21 C.F.R. § 601.12(b)(2)(i) (referencing changes in qualitative or quantitative formulation or in the specifications provided in the approved application). *See also* 21 C.F.R. §211.110(a)(), (b) (referencing "in-process specifications" applicable to drug product "weight variation"); Ex. 22, FDA Guidance for Industry, *Changes to an Approved NDA or ANDA, Questions and Answers*, at 9 (Jan. 2001) ("A change in the fill volume of a drug product involves a change to the specification and must be submitted in a prior approval supplement.").

IV. Standard for Summary Judgment

Summary judgment is proper only if "there is no genuine issue as to any material fact, and the moving party is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(c). The moving party bears the burden of showing that no genuine issue of material fact exists. *See Zamora v. Elite Logistics, Inc.*, 449 F.3d 1106, 1112 (10th Cir. 2006). The Court resolves all factual disputes and draws all reasonable inferences in favor of the non-moving party. *Id.* However, the party seeking to overcome a motion for summary judgment may not "rest on mere allegations" in its complaint but must "set forth specific facts showing that there is a genuine issue for trial." Fed. R. Civ. P. 56(e). The party seeking to overcome a motion for summary judgment must also make

a showing sufficient to establish the existence of those elements essential to that party's case. *See Celotex Corp. v. Catrett*, 477 U.S. 317, 323-33 (1986).

V. Preemption Law

Preemption analysis requires the court to compare federal and state law. *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 611 (2011). If a private party cannot comply with state law without first obtaining the approval of a federal regulatory agency, the application of the state law to that private party is preempted. *Id.* at 620 (stating that "[t]he question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it."). The Court's "inquiry into the scope of a [federal] statute's pre-emptive effect is guided by the rule that the purpose of Congress is the ultimate touchstone in every pre-emption case." *Hughes v. Talen Energy Mktg., LLC*, 136 S. Ct. 1288, 1297 (2016) (citing U.S. Const., Art. VI, cl. 2 and *Altria Group, Inc. v. Good*, 555 U.S. 70, 76 (2008)).

Preemption may be express or implied. Implied preemption may take the form of either obstacle preemption—which is applicable if state law "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress"—or impossibility preemption—which is applicable if it would be "impossible for a private party to comply with both state and federal requirements." *In re Universal Service Fund Telephone Billing Practice Litig.*, 619 F.3d 1188, 1196 (10th Cir. 2010). The federal requirements may be imposed by federal statutes or regulations. *See Fid. Fed. Sav. & Loan Ass'n. v. de la Cuesta*, 458 U.S. 141, 153 (1982). The state law subject to preemption may be state statutes, regulations, or duties imposed by tort claims or other court actions. *See Riegel v. Medtronic, Inc.*, 552 U.S. 312, 324-25 (2008); *Geier v. American Honda Motor Co., Inc.*, 529 U.S. 861, 881 (2000).

Impossibility preemption is applicable when a private party cannot "*independently* do under federal law what state law requires of it." *PLIVA, Inc. v. Mensing,* 564 U.S. 604, 620 (2011)

(citing *Wyeth v. Levine*, 555 U.S. 555, 573 (2009) (emphasis added)). In other words, "[i]f a private party . . . cannot comply with state law without first obtaining the approval of a federal regulatory agency, then the application of that law to that private party is preempted." *Gustavsen v. Alcon Laboratories*, 903 F.3d 1, 9-10 (lst Cir. 2018).

VI. Analysis

Plaintiffs' Third Amended Complaint alleges Genentech has breached warranties and violated California consumer protection statutes by falsely claiming that (1) each Herceptin vial contains 440 mg of trastuzumab; (2) if a vial of Herceptin is reconstituted according to defendant's instructions, it will yield a solution with a concentration of 21 mg/mL of trastuzumab (the "Solution"); and (3) each vial of reconstituted Herceptin contains 20.952 mL of solution. Plaintiffs challenge the accuracy of Herceptin's labeling concerning the amount of trastuzumab in the vials, whether measured as weight, volume or weight per milliliter.[5]

Genentech contends that Plaintiffs' claims are impliedly preempted because they seek to impose (1) a state-law requirement that would stand as an obstacle to the federal regulatory scheme, which recognizes reasonable variation in manufacturing and labeling must be allowed (*i.e.*, "obstacle preemption") and (2) a state-law duty on Genentech to change either its manufacturing processes or its Herceptin labeling, neither of which it can do under federal law without prior FDA approval ("impossibility preemption").

Specifically, Genentech argues Plaintiffs' state-law claims present an obstacle to the federal regulatory scheme for branding of prescription drugs—*i.e.*, 21 U.S.C. § 352(b) and 21

[5] Milligrams (mg) measure weight, and one mg is 1/1000 of a gram; milliliters (ml) measure volume of liquid, and one ml is 1/1000 of a liter; and mg/mL measures milligrams per milliliter.

C.F.R. § 201.51(g).[6] It asserts that (1) Herceptin complies with federal labeling laws, which allow for reasonable variations in manufacture and labeling; and (2) Plaintiffs may not use state law claims to impose a more stringent standard than federal law allows. Additionally, Genentech contends that Plaintiffs' claims are barred by impossibility preemption because, in order to meet Plaintiffs' demands, it would have to change either the product labeling or the reconstituted solution volume—both of which would require FDA approval.

Plaintiffs, however, argue that neither obstacle preemption nor impossibility preemption bar their claims because the FDA has incorrectly regulated Herceptin as a "solid drug" rather than a "liquid drug;" the FDA's 2014 Draft Guidance stating that the labeling of all injectable drugs, including those reconstituted from a solid, should be applied retroactively; and Herceptin did not

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[6] 21 U.S.C. § 352(b) states that a drug shall be deemed misbranded--:

> If in package form unless it bears a label containing . . . (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count: *Provided*, That under clause (2) of this paragraph **reasonable variations shall be permitted**, and exemptions as to small packages shall be established, by regulations prescribed by the Secretary. (emphasis added).

21 C.F.R. § 201.51(g) states:

> The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. Reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized. Variations from stated quantity of contents shall not be unreasonably large. In the case of a liquid drug in ampules or vials, intended for injection, the declaration shall be considered to express the minimum quantity and the variation above the stated measure shall comply with the excess volume prescribed by the National Formulary or the U.S. Pharmacopeia for filling of ampules. **In the case of a solid drug in ampules or vials, the declaration shall be considered to express the accurate net weight. Variations shall comply with the limitations provided in the U.S. Pharmacopeia or the National Formulary.** (emphasis added).

meet § 201.51(g)'s allowance for "[r]easonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing."

A. Obstacle Preemption

Genentech argues all of Plaintiffs' claims are barred because they impose an obstacle to the FDA's "reasonable variations" determination and are inconsistent with federal law. Plaintiffs assert obstacle preemption is inapplicable because (1) their claims do not conflict with federal law; (2) Genentech is violating federal law; and (3) even if the Court grants summary judgment on their net weight claims, their concentration and solution volume claims should survive, because neither obstacle preemption nor impossibility preemption apply to the remaining two claims.

1. Plaintiffs' Claims Impose an Obstacle to the FDA's "Reasonable Variations" Determination

Federal law prohibits the manufacture, introduction or delivery of any drug that is adulterated or "*misbranded.*" 21 U.S.C. § 331(a), (g) (emphasis added).

Although package labels must contain "an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count," the applicable statute permits "reasonable variations" pursuant to regulations prescribed by the FDA. 21 U.S.C. § 352(b)(2). FDA regulations, in turn:

- permit "reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice;"
- provide that, "in the case of a solid drug in ampules or vials, the declaration shall be considered to express the accurate net weight;" and
- state that "[v]ariations shall comply with the limitations provided in the U.S. Pharmacopeia or the National Formulary."

21 C.F.R. § 201.51(g). *Id.*

With respect to packaged food and drugs, the Supreme Court has recognized there is no way to completely eliminate variations in weight, and that to require strict precision would make it impossible to sell packaged products. In *Jones v. Rath Packing Co.*, it stated:

> It being apparent to everyone that it is impossible to make packages of exactly the same size or to pack them with exactly the same quantity of contents, and it being also apparent that the exact weight and measure of the contents of a package may undergo slight changes from natural causes, it is also apparent that legislation requiring similar packages to contain the same exact quantity in term of weight or measure, without allowing for any variation, would be destructive and prevent the putting of foods in packages.

430 U.S. 519, 5367, n.28 (1977) (quoting H.R. Rep. No. 850, 62d Cong., 2d Sess., at 2; S. Rep. No. 1216, 62d Cong., 3d Sess., at 2-3). In *Jones*, a meat processor and flour millers argued a California statute and regulation pertaining to the labeling by weight of packaged foods were preempted by federal laws regulating net weight labeling. The Court interpreted those regulations to mean that "[u]nder the FDCA, *reasonable variations from the stated net weight do not subject [the defendant] to prosecution, whether civil or criminal*, if the variations arise from the permitted causes." *Id.* at 536 (emphasis added). The Court stated:

> Since 1914, regulations under the food and drug laws have permitted reasonable variations from stated net weight resulting from packing deviations or gain or loss of moisture occurring despite good commercial practice. If Congress had intended to overrule this longstanding administrative practice, founded on a legislative statement of necessity, we would expect it to have done so clearly. Instead, it explicitly preserved existing law, with "no changes."

Id. at 537. Accordingly, the Court held that enforcement of more stringent state law was preempted because it would "prevent the accomplishment and execution of the full purposes and objectives of Congress . . ." *Id.* at 543.

FDA regulations provide that the labeling for a prescription drug must include a statement of the net quantity of contents. 21 C.F.R. § 201.51(a). The declaration of net quantity allows for reasonable variations because of loss or gain of moisture during the course of good distribution

practice and unavoidable deviations in good manufacturing practice. *Id.*, §210.51(g). The variations must comply with the limitations of the USP or the *National Formulary. Id.*

The description of the net quantity of contents required by FDA regulations depends on how the drug is supplied. Injectable drug products may be liquids in the form of solutions, emulsions or suspensions, or dry solids that are to be combined with an appropriate liquid to yield a solution or suspension.[7] FDA net quantity labeling regulations distinguish between liquid and solid drugs:

> The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. *Reasonable variations caused by loss or gain of moisture during the course of good distribution practice or by unavoidable deviations in good manufacturing practice will be recognized.* Variations from stated quantity of contents shall not be unreasonably large. *In the case of a liquid drug in ampules or vials, intended for injection, the declaration shall be considered to express the minimum quantity and the variation above the stated measure shall comply with the excess volume prescribed by the National Formulary or the U.S. Pharmacopeia for filling of ampules. In the case of a solid drug in ampules or vials, the declaration shall be considered to express the accurate net weight.* Variations shall comply with the limitations provided in the U.S. Pharmacopeia or the National Formulary.

21 C.F.R. § 201.51(g) (emphasis added). Thus, while the label for liquid drugs must express the *minimum* quantity, the label for Herceptin—a solid drug—is considered to express the "accurate net weight" of the drug.

Here, as in *Jones*, Plaintiffs' labeling claims conflict with federal law, which permits reasonable variations for solid drugs sold in vials. Nor is the Court swayed by Plaintiffs' assertion that *Wyeth v. Levine*, 555 U.S. 555 (2009) compels a different conclusion. In *Wyeth*, the Supreme

[7] Doc. 201-5, Ex. 5, Lin Dec., ¶26 (citing FDA Guidance for Industry (Draft), Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, p. 11, April 2013; FDA-CDER-SBIA Regulatory Education for Industry, Prescription Drug Labeling – Challenges and Issues: Common Deficiencies in Container Labels and Carton Labeling for Biological Products, November 2015.

Court held that a plaintiff's failure-to-warn claims were not preempted because federal regulations allowed the manufacturer of an anti-nausea medication to *unilaterally* strengthen warnings on the medication. *Id.* at 568. Here, in contrast, the regulatory scheme expressly allows a range of "reasonable variations" for solid drugs sold in vials, and Plaintiffs' state-law claims conflict with these regulations.

2. Plaintiffs' Claims are Inconsistent with Federal Law

a. Herceptin is a Solid Drug

Plaintiffs argue that Herceptin should be considered a "liquid drug" subject to the requirement that the label "express the minimum quantity" as a measure of volume, rather than as a "solid drug." However, regulatory history establishes that the FDA has always considered Herceptin to be a "solid drug." The FDA approved the BLA with a label that referenced a net weight of 440 mg and a fill weight specification allowing deviations both above and below 440 mg. (Doc. 377-14, Def. Ex. 14, Dep. of David T. Lin, at 139:2-12 ("When [Herceptin] was approved in 1998, FDA treated it as a solid drug."). Moreover, the FDA has repeatedly approved this labeling for nearly two decades, and when it approved the updated labeling in 2017, it inserted the phrase "for injection" next to the product name "HERCEPTIN® (trastuzumad),"[8] thereby reaffirming that it considers Herceptin to be a solid drug. Doc. 377-15, Def. Ex. 15.[9]

[8] The U.S. Pharmacopeia National Formulary distinguishes between drugs that are designated "injection" and those designated "for injection." "Injection drugs" are "[l]iquid preparations that are drug substances or solutions thereof," while "for injection drugs" are sold as "[d]ry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for injections. Doc. 372-10, Pls. Ex. 80 at 3.

[9] Plaintiffs also argue that even if Herceptin is a "solid drug" for purposes of § 201.51(g), Genentech has not proven it exercised "good manufacturing practice" with respect to the drug product strength, the variations in Herceptin strength were reasonable, or variations below 440 mg of trastuzumab were caused by "unavoidable deviations in good manufacturing," and therefore

b. The FDA's 2014 Draft Guidance is not Retroactive

Plaintiffs also contend that the Court should give deference to the FDA's conclusion in 2014 that Herceptin labeling did not comply with the 2014 Draft Guidance, in which it stated that the labeling of all injectable products, including those reconstituted from a solid, must reflect the minimum quantity of drug product that can be withdrawn from the vial. However, this argument is based on Plaintiffs' faulty premise that the Draft Guidance merely restated standards in place since the FDA originally approved Herceptin's BLA in 1998. As the regulatory history of Herceptin establishes, this is not true.

Moreover, from a legal stand point, Guidances are prospective in nature absent a contrary instruction from the FDA. Doc. 201-5, Ex. 5, Lin Dec., ¶¶62-71.[10] The Draft Guidance itself states that its recommendations "apply to new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologics license applications (BLAs), as well as new packaging supplement to these existing applications submitted to CDER and CBER." Doc. 368-31, Pls. Ex. 31, FDA Draft Guidance for Industry, *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biologic Products*, at 1 (March 2014). Here, there is no dispute that the BLA for Herceptin was approved more than 15 years before the 2014 Draft Guidance was issued.

Finally, Plaintiffs' argument ignores Herceptin's approval history. The uncontroverted facts establish the FDA-approved BLA disclosed that although the protein content label claim was 440 mg, the vials were intended to deliver only 400 mg, and that in 1999, the FDA drafted a letter

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Genentech's Motion for Summary Judgment must be denied. Doc. 368 at 50. However, these arguments clearly go to the merits of Plaintiffs' claims rather than the issue of preemption.

[10] The Draft Guidance states that "[t]his draft guidance, when finalized, will represent the [FDA's] current thinking on this topic. It does not create or confer any right for or on any person and does not operate to bind FDA or the public." Doc. 368-31, Pls. Ex. 31, p. 1.

to providers explicitly referring to the fact that the vial was designed to deliver 400 mg. It was not until 2014 that the FDA raised concerns about the labeling of Herceptin, and although Genentech promptly submitted proposed revisions, the FDA waited until 2017 to respond to Genentech's proposal.[11]

Accordingly, the Court declines to apply the FDA's Draft Guidance retroactively.

c. Herceptin's Protein Content Variations Satisfied FDA Regulatory Requirements

Net quantity labeling for solid drugs is governed by 21 C.F.R. § 201.51(g), which states:

> The declaration of net quantity of contents shall express an accurate statement of the quantity of contents of the package. *Reasonable variations caused by loss or gain of moisture during the course of good distribution practice by unavoidable deviations in good manufacturing practice will be recognized. Variations from stated quantity of contents shall not be unreasonably large.* In the case of a liquid drug in ampules or vials, intended for injection, the declaration shall be considered to express the minimum quantity and the variation of above the stated measure shall comply with the excess volume prescribed by the National Formulary or the U.S. Pharmacopeia for filling of ampules. *In the case of a solid drug in ampules or vials, the declaration shall be considered to express the accurate net weight. Variations shall comply with the limitations provided in the U.S. Pharmacopeia or the National Formulary.*

(emphasis added). The regulatory history of Herceptin clearly establishes that the FDA considers it to be a solid drug. It is undisputed that the protein content of the Herceptin 440 mg vials has always been within the total protein specification of 440 mg ± 35 mg (405 mg to 475 mg) approved by the FDA. Thus, at all relevant times, Genentech complied with the unambiguous terms of Section 201.51(g).

[11] Arguably, retroactive application of the 2015 Final Guidance to impose tort liability would violate due process. *See United States v. AMC Entm't*, 549 F.3d 760, 768-70 (9th Cir. 2008) (rejecting retroactive application of government's interpretation of ADA regulations to movie theaters).

d. Herceptin Was Not "Adulterated"

Plaintiffs argue that Herceptin is adulterated under 21 U.S.C. § 341 because "its strength differs from . . . that which it purports or is represented to possess." Doc. 368 at pp. 45-46 (quoting Ex. 81, FDC Compliance Policy Guide ("CPG") § 420.100). However, CPG § 420.100 provides: "[t]he applicable quality standards for a drug not recognized in an official compendium can be determined from such sources as the labeling of the drug (or drug product), the manufacturer's written specifications, and new drug applications." *Id.*

In this case, the FDA-approved Prescribing Information does not state that Herceptin vials contain exactly 440 mg, but instead that they "*nominally* contain[] 44 mg Herceptin." Doc. 201-1, Ex. 1 at 1 (emphasis added). Likewise, since at least April 2000, the carton label has stated that "[t]he *nominal* content of each HERCEPTIN vial is 440 mg Trastuzumab." Doc. 201-7, Ex. 7 (emphasis added).

3. Plaintiffs' "Concentration" and "Solution Volume" Claims Do Not Survive

The Court rejects Plaintiffs' arguments that Herceptin is a "liquid drug" rather than a "solid drug," and that it should be subjected to the "liquid drug" requirement that the labeling "express the 'minimum quantity' as a measure of volume" instead of the "solid drug" requirement that the labeling "express accurate net weight" with USP-compliant variations. The undisputed facts establish that the FDA has always treated Herceptin as a solid drug, and has allowed reasonable variations as provided in the USP. Additionally, USP General Chapter <905>, *Uniformity of Dosage Units*, provides for an allowable variation of 15% around the label claim. 21 C.F.R. § 201.51(g). Def. Ex. 5, Lin Dec. ¶29, Ex. D to Lin Dec. at 491. Therefore, like their "net weight" claim, Plaintiffs' "concentration" and "solution volume" claims also fail.

Accordingly, Plaintiffs' claims are barred by obstacle preemption.

B. Impossibility Preemption

Plaintiffs contend Genentech could comply with its state law-based demands by changing either the manufacturing process or the labeling of Herceptin.

Genentech, however, argues that Plaintiffs' claims fail as a matter of law under the doctrine of impossibility preemption, because ensuring that each vial contains exactly (or at least) 440 mg, as Plaintiffs demand, would have required Genentech to change its manufacturing process, its protein content specification and its labeling, all of which would require prior FDA approval.

It is undisputed that Genentech would be required to make changes to manufacturing and specifications—both necessitating prior FDA approval—to ensure that all Herceptin vials contained at least 440 mg. Changing the target fill weight, which is an in-process specification identified in the BLA, requires prior FDA approval. Doc. 377, Ex. 14, Lin Dep. at 141:1-25; 21 C.F.R. § 601.12(b)(2)(i); 21 C.F.R. § 211.110(a)(1)(b) (referencing "in-process specifications" applicable to drug product "weight variation"); Doc. 377, Ex. 22, FDA Guidance for Industry, *Changes to an Approved NDA or ANDA, Questions and Answers*, at 9 (Jan. 2001) ("A change in the fill volume of a drug product involves a change to the specification and must be submitted in a prior approval supplement. . . ."). *See also Gustavsen*, *supra* (affirming district court's dismissal of case asserting that eye drop manufacturer's practice of using eye drop dispensers that emit unnecessarily large drops was unfair and resulted in unjust enrichment because the manufacturing changes plaintiffs sought would require prior FDA approval); *Thompson v. Allergan U.S.A., Inc.*, 933 F. Supp. 2d 1007, 1013-14 (E.D. Mo. 2014) (granting motion to dismiss based on federal preemption because changing the fill volume in each vial of eye drops would require prior FDA approval).

Plaintiffs also suggest that Genentech could have changed from the originally approved static filling process to a variable filling method to ensure 440 mg per vial. Doc. 368 at 79 (citing Ex. 2, Ramirez Dec., ¶¶ 32-33). However, this would still require prior FDA approval because the manufacture of Herceptin is an aseptic (sterile) processing operation. Doc. 377, Ex. 17, GENE-FL0000000527-529, 555. Substituting steps in an aseptic processing operation is a "Major change" requiring prior FDA approval. 21 U.S.C. § 601.12(b)(2)(vi). Additionally, Defendant would be required to change the Herceptin labeling to reflect the change in diluent volume. *See* 21 C.F.R. § 601.12(f)(1); Doc. 201, Ex. 5, Lin Dec., ¶¶ 75-76.

Finally, Plaintiffs contend that Genentech could have changed its label to state the accurate concentration for reconstituted Herceptin solution. Changing the concentration stated on the label, however, would require FDA approval. 21 C.F.R. § 601.12(f)(1). Similarly, changing the concentration of the reconstituted drug product would also require FDA approval because it would have "a substantial potential to have an adverse effect on the . . . strength [and] potency" of Herceptin and affect the "safety or effectiveness of the product." 21 C.F.R. § 601.12(b)(1) and (2)(i).

C. Stop Selling

Finally, Plaintiffs argue that Genentech could comply with state law by keeping its manufacturing process the same, but selling only those vials that contain at least 440 mg of trastuzumab. Doc. 368 at 68-69. This "stop-selling" argument, however, was squarely rejected in *Mutual Pharmaceutical Co. v. Bartlett*, 570 U.S. 472 (2013). There, the Supreme Court stated:

> Our pre-emption cases presume that an actor seeking to satisfy both his federal-and state-law obligations is not required to cease acting altogether in order to avoid liability. Indeed, if the option of ceasing to act defeated a claim of impossibility, impossibility pre-emption would be "all but meaningless."

> The incoherence of the stop-selling theory becomes plain when viewed through the lens of our previous cases. In every instance in which the Court has found impossibility pre-emption, the "direct conflict" between federal- and state-law duties could easily have been avoided if the regulated actor had simply ceased acting.

Id. at 488 (quoting *PLIVA*, 564 U.S. at 620). The Court cited *PLIVA* as an obvious example:

> [T]he *PLIVA* Court held that the state failure-to-warn claims were preempted by the FDCA because it was impossible for drug manufacturers to comply with both the state-law duty to label their products in a way that rendered them reasonably safe and the federal-law duty not to change their drugs' labels. It would, of course, have been possible for drug manufacturers like PLIVA to pull their products from the market altogether. In so doing, they would have avoided liability under both state and federal law: such manufacturers would neither have labeled their products in a way that rendered them unsafe nor impermissibly changed any federally approved label.

Id. (citation omitted).

Similarly, in this case, Genentech cannot be forced to stop selling vials that comply with FDA requirements in order to avoid liability under state law claims.

V. Conclusion

For the reasons set forth above, Defendant's Motion for Summary Judgment Based on Federal Preemption (Doc. 201), is hereby granted.

ENTERED this 20th day of March, 2019.

Terence C Kern

TERENCE C. KERN
United States District Judge